CHRONIC TOXICITY SUMMARY

CARBON DISULFIDE

(carbon bisulfide; carbon sulfide; dithiocarbonic anhydride)

CAS Registry Number: 75-15-0

I. Chronic Toxicity Summary

Inhalation reference exposure level	**800 µg/m^3** (300 ppb)
Critical effect(s)	CNS/PNS (reduction in motor nerve conduction velocities in occupationally-exposed humans)
Hazard index target(s)	Nervous system; reproductive system

II. Physical and Chemical Properties Summary (HSDB, 1995; CRC, 1994)

Description	Clear, colorless or faintly yellow liquid
Molecular formula	CS_2
Molecular weight	76.14 g/mol
Boiling point	46.5°C
Melting point	−111.5 °C
Vapor pressure	297 torr @ 20°C
Solubility	Slightly soluble in water (2.94 g/L); miscible in anhydrous methanol, ethanol, ether, benzene, chloroform, and carbon tetrachloride
Conversion factor	3.1 mg/m^3 per ppm at 25°C

III. Major Uses and Sources

The most prominent industrial use of carbon disulfide is in the production of viscose rayon fibers. Carbon disulfide is also used in the production of carbon tetrachloride and cellophane, and, as a solvent for rubber, sulfur, oils, resins, and waxes. In the past, carbon disulfide was used in soil fumigation and insect control in stored grain. Industrial processes that produce carbon disulfide as a by-product include coal blast furnaces and oil refining (HSDB, 1995). Carbon disulfide is also a breakdown product of metam sodium. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1562 pounds of carbon disulfide (CARB, 2000).

IV. Effects of Human Exposure

A primary target of carbon disulfide (CS_2) toxicity is the nervous system. The major neurotoxic action of carbon disulfide is the development of mental disturbances. These include change of personality, irritability, and forgetfulness, often with accompanying neurophysiological and neuropathological changes after prolonged exposure. Such changes include decreased peripheral nerve impulse conduction, motor and/or sensory neuropathies, cerebral or cerebellar atrophy, and neuropsychological organic changes (Aaserud *et al.* 1988, 1990, 1992; Foa *et al.*, 1976; Hirata *et al.* 1992; Ruijten *et al.* 1990, 1993). Alterations in behavioral indices have historically been associated with high levels of CS_2, often in excess of 20 ppm (Foa *et al.* 1976; Hanninen *et al.*, 1978).

Studies have identified alterations in the nerve conduction of workers chronically exposed to lower CS_2 levels (Hirata *et al.*, 1992a; Johnson *et al.*, 1983; Ruijten *et al.*, 1990; Ruijten *et al.*, 1993). A cross-sectional study of Japanese spinning workers identified alterations in the central nervous system as measured by brain stem auditory evoked potential (BAEP) (Hirata *et al.*, 1992). The latencies of the three main BAEP components increased significantly in workersexposed to CS_2 for more than 20 years when compared to controls. CS_2 exposures ranged from 3.3 to 8.2 ppm (mean = 4.76 ppm). Ruijten *et al.* (1993) identified mild presymptomatic nerve impairment (decreased conduction velocities and response amplitudes) in 44 CS_2-exposed workers with an average cumulative exposure range from 192 to 213 ppm-year (mean duration = 26.1 years).

A NIOSH occupational study evaluated the effects of CS_2 on the peripheral nervous system. Johnson *et al.* (1983) identified a significant dose related reduction in the maximum motor nerve conduction velocities (MCV) in the calves and ankles of male viscose rayon workers exposed to high (median = 7.6 ppm) CS_2 levels versus a comparison group exposed to low concentrations (median = 0.2 ppm). The workers were all employed in artificial fiber production in the same plant. Since these reduced MCVs were still within the normal range, the authors considered the measured difference an indication of minimal neurotoxicity. The mean exposure concentration for all exposed workers (n = 145) ranged from 0.6 to 16 ppm (mean = 7.6 ppm) with a mean duration of 12.1 years. This study identified a chronic LOAEL of 7.6 ppm for minor neurological effects (decreased peroneal nerve MCV and sural nerve conduction velocity).

Another epidemiological study evaluated a group of 111 Belgian viscose rayon factory workers exposed to 4 to 112 mg/m^3 CS_2 (time-weighted average 1 to 40 mg/m^3) (Vanhoorne et al., 1995). Among four categories of cumulative exposure (0, 1 to 300, 301 to 600, and greater than 600 mg/m^3-years), a clear dose-response effect was observed for reduced mean peroneal motor nerve conduction velocities in both fast and slow fibers. Unfortunately, the data are incompletely reported, and the mean duration of exposure is not given. Subgroups of workers whose exposures ever exceeded 10 ppm (n=64) and never exceeded 10 ppm (n=30) each showed significantly reduced fibular nerve motor conduction velocities compared with non-exposed workers.

Vascular atherosclerotic changes are also considered a major effect of chronic carbon disulfide exposure. Several occupational studies have demonstrated an increase in the

mortality due to ischemic heart disease in CS_2 exposed workers (Hernberg *et al.*, 1970; MacMahon and Monson, 1988; Tiller *et al.*, 1968; Tolonen *et al.*, 1979). A 2.5-fold excess in mortality from coronary heart disease in workers exposed to CS_2 was first reported by Tiller *et al.* (1968). A subsequent prospective study by Hernberg *et al.* (1970) found a 5.6-fold increased risk in coronary heart disease mortality and a 3-fold increased risk of a first nonfatal myocardial infarction in CS_2 exposed workers.

Male workers (n=177) in a Polish fiber plant were exposed to CS_2 for an average of 14 years (range of 5 to 38 years). Controls were 93 healthy male workers from other factories that did not use carbon disulfide. Carbon disulfide exposed workers had higher rates (42%) of 24-hour electrocardiographic abnormalities than non-exposed workers (24%, p=0.006) (Bortkiewicz et al., 2001). The most common abnormalities were ventricular extrasystoles and repolarization disturbances, the latter occurring most often in workers with the longest CS_2 exposures. Long-term blood pressure monitoring did not reveal any differences between exposed and control groups.

Male workers in a Belgian viscose rayon factory (n=85) were estimated by personal active sampling to have exposures of 2 to 32 mg/m^3 CS_2. Controls were 37 non-exposed workers from factories that did not use CS_2. Exposed workers had reduced common carotid artery distensibility as measured with ultrasound sonography, while the carotid artery compliance coefficient was not significantly affected. Also, blood pressures and cholesterol levels were not significantly different than observed among control workers (Kotseva et al., 2001a). Differences in carotid artery distensibility remained significant after adjustment for age, smoking, alcohol consumption, ethnicity, body mass index, heart rate, and systolic blood pressure.

Egeland *et al.* (1992) and Vanhoorne *et al.* (1992) have reported that human exposure to CS_2 for more than one year causes increases in biochemical changes often associated with cardiovascular disease - diastolic blood pressure, low density lipoprotein cholesterol, and apolipoproteins A1 and B. Egeland *et al.* (1992) used cross sectional data on 165 CS_2-exposed workers (245 controls) collected in 1979 by Fajen *et al.* (1981). The affected workers were exposed for at least 1 year in a viscose rayon factory to an estimated median TWA (8-hour) of 7.6 ppm. The Egeland *et al.* (1992) study indicated that modest CS_2 exposure (range = 3.4 to 5.1 ppm, median = 4.1 ppm) was associated with increased low density lipoprotein cholesterol (LDLc), the type of increase associated with atherosclerotic heart disease. No significant differences were seen between controls and the low CS_2 exposed group (range = 0.04 to 1.02 ppm, median = 1.00 ppm). Study NOAEL and LOAEL for increased LDLc and diastolic blood pressure were thus 1.0 ppm and 4.1 ppm , respectively. Vanhoorne *et al.* (1992) identified increased LDL-cholesterol, apolipoprotein B, systolic and diastolic blood pressure as indicative of an increased coronary risk in workers from a Belgian viscose rayon factory (115 exposed and 76 controls). CS_2 concentrations ranged from 1 to 36 ppm. Duration of exposure was not indicated. Even though these biochemical changes were observed, no significant increases in cardiovascular disease, such as angina, myocardial infarction, or ischemia, were determined by ECG changes.

Workers (n=141) with a minimum of 1 year employment in viscose rayons factories were compared with 141 age and gender-matched plastic industry workers. Current exposures were estimated as 1 to 30 mg/m^3 (03 to 10 ppm). Exposed workers were categorized as group 1 or group 2, with cumulative exposures of less than or greater than 100 mg/m^3-years, respectively. Group 2 ($p<0.001$) but not group 1 workers had increased mean total cholesterol (5.3 and 4.5 mmol/l) compared with controls (4.6 mmol/l) (Kotseva, 2001b).

CS_2 causes reproductive toxicity in both males and females. Lancranjan *et al.* (1969), Lancranjan (1972), Cirla *et al.* (1978), and Wagar *et al.* (1983) studied male reproductive effects of occupational exposure to CS_2 and showed significant adverse effects on spermatogenesis, levels of serum FSH and LH, and libido; these effects persisted in 66% of the workers subject to follow-up. Zhou *et al.* (1988) investigated pregnancy outcomes and menstrual disturbances in 265 women occupationally exposed to CS_2 in five facilities and 291 controls. The CS_2-exposed women had a significantly higher incidence of menstrual disturbances versus the control group (overall 34.9% vs. 18.2%). CS_2 levels varied between the five facilities (exposure category means of low = 3.1 mg/m^3, intermediate = 6.5 mg/m^3, and high = 14.8 mg/m^3), but all workers from these CS_2 facilities had significantly higher incidences of menstrual disturbance. Irregularity of menstruation was the most common disturbance, followed by abnormal bleeding. No evidence was observed to indicate an adverse effect on the term and outcome of pregnancy.

An abstract of an epidemiological study of birth defects among female workers occupationally exposed to CS_2, was reported by Bao et al. (1991). Exposures were at rayon factories in four Chinese provinces and began at least 6 months prior to pregnancy and continued during pregnancy. An increased rate of birth defects (2.6% vs. 1.3%) among 682 exposed women was noted compared to 745 women in the control group. The most common defects were congenital heart defects, inguinal hernia, and CNS defects. However, there was no significant difference in birth defects between those with estimated exposures greater than 10 mg/m^3 compared to those with lower exposures. There were no differences in rates of stillbirth, low birth weight, or neonatal or perinatal deaths among any of the groups.

The possibility of determining LOAEL and/or NOAEL values for the major CS_2-related adverse effects from epidemiology studies, which predominately use workers from the viscose rayon industry, is limited. The limitations include incomplete historical exposure measurements, concurrent exposure to other chemicals (including hydrogen sulfide or methylene chloride), lack of personal exposure determinations, and a high variability of individual exposures due to decreases of plant CS_2 concentrations over time.

V. Effects of Animal Exposure

Studies investigating the potential for CS_2 toxicity in animals have usually been limited by intermediate or subchronic duration (less than 1 year) and a lack of multiple dose or

exposure groups. The neuropathologic changes consistently observed in rodents following CS_2 exposure include axonal swelling, demyelination, swelling at neuromuscular junctions, muscle atrophy and degeneration, damage to terminal axons, and nerve fiber breakdown (Clerici and Fechter, 1991; Colombi *et al.* 1981; Eskin *et al.*, 1988; Jirmanova and Lukas, 1984; Maroni *et al.*, 1979; Szendzikowski *et al.*, 1973). These adverse effects have been observed over a range of exposures (250 to 800 ppm), but few studies have attempted to establish a dose response for this CS_2-induced neurotoxicity.

In a 90 day subchronic inhalation study, Sprague-Dawley and Fischer 344 rats exposed discontinuously (6 hours/day, 5 days/week) to CS_2 developed morphological alterations in nerves including axonal swelling and myelin degradation (Gottfried *et al.*, 1985). This study established a subchronic NOAEL of 50 ppm and a LOAEL of 300 ppm for morphological changes in nerves. A longer inhalation study in Wistar rats observed impairment in the conduction velocity of the sciatic and tibial nerves after 6 and 12 months of intermittent exposure to 289 ppm CS_2 (LOAEL of 289 ppm) (Knobloch *et al.*, 1979).

In a 13-week subchronic study, male and female F344 rats inhaled 0, 50, 500, or 800 ppm CS_2 discontinuously (6 h/day, 5 days per week) (Sills *et al*.,1998). Development of distal axonopathy in the muscular branch of the posterior tibial nerve (MBPTN) and spinal cord was examined. After 13 weeks, giant swollen axons were observed with thin myelin sheaths as well as some degenerated and regenerated axons. Axonal swelling was noted in the spinal cords of rats exposed to 500 or 800 ppm CS_2. In the 800 ppm group, additional axonal swelling was observed in the muscular branch of the posterior tibial nerve, . Neurofilament deposits were found in swollen axons in the spinal cord and MBPTN. The NOAEL for axonal swelling was 50 ppm.

Wronska-Nofer (1973) showed a positive relationship between the level of triglycerides, the rate of cholesterol synthesis, and CS_2 exposure in Wistar rats exposed to 0, 73.8, 160, 321, or 546 ppm CS_2 for 5 hours/day, 6 days/week over 8 months. This study found a subchronic LOAEL of 73.8 ppm for disturbances in lipid metabolism (increase in serum cholesterol and serum triglycerides).

Lewis *et al*. (1999) investigated the capacity of CS_2 to induce arterial fatty deposits by itself, and its ability to enhance the rate of fatty deposit formation induced by a high fat diet. Groups of 20 female C57BL/6 mice were exposed to 0, 50, 500, or 800 ppm CS_2 by inhalation. Half the animals in each group were placed on an atherogenic high fat diet and half on a control diet. Mice were necropsied after 1, 4, 8, 12, 16, or 20 weeks of exposure, and the rates of fatty deposit formation under the aortic valve leaflets were evaluated. Exposure of mice on the control diet to 500 and 800 ppm CS_2 induced a small but significant increase in the rate of fatty deposit formation over non-exposed controls. In the animals on the high fat diet there was marked enhancement of the rate of fatty deposit formation in mice exposed to 500 and 800 ppm over the animals on the high fat diet alone. In addition, there was a small but significant enhancement in mice exposed to 50 ppm over the rate of fatty deposit formation induced by the high fat diet alone. Thus

CS_2 is atherogenic at high concentrations and in conjunction with other risk factors, CS_2 at relatively low concentrations can enhance atherogenesis in mice. Fifty ppm is thus the study LOAEL.

Hepatic toxicity has also been induced in rats exposed to relatively high doses of CS_2, usually following pretreatment with liver inducers such as phenobarbital. Bond *et al.* (1969) showed that high doses of CS_2 to rats produced an increase in periportal liver fat, and decreases in hepatic cytochrome P450 content and in microsomal mixed function oxidase (MFO) activity. After phenobarbital induction, exposed rats exhibited more severe hepatoxicity characterized by hydropic degeneration and necrosis. Other hepatotoxic effects seen after CS_2 exposures greater than 400 ppm include increases in relative liver weight (Sokal, 1973), stimulation of liver microsomal lipid peroxidation (Wronska-Nofer *et al.*, 1986), and decreases in hepatic cholesterol synthesis (Simmons *et al.*, 1988).

The 24-hr lethal ip LD_{50} values for CS_2 were estimated in 1-, 5-, 10-, 20-, 30- and 40-day-old rats (sample size not specified) (Green and Hunter, 1985). 1-day-old rats (LD_{50} 583 mg/kg, ip) were about 3-times more susceptible than 20-day-old rats (LD_{50} 1545 mg/kg, ip).

^{14}C- and ^{35}S-labelled CS_2 was given ip to 1-, 5-, 10-, 20-, 30-, and 40-day-old rats (Snyderwine and Hunter, 1987). Thirty- and forty-day-old rats (sample size not reported) metabolized significantly more CS_2 to CO_2 and expired significantly less CS_2 than 1- to 20-day-old rats. Twenty-four hr after administration, up to 13 times more ^{35}S -label (radioactivity per g of tissue) were present in organs from 1-day-old rats than in similar organs from 40-day-old rats. The study does not specifically address the toxicological implications of the metabolic differences, and did not include fully mature animals. However, inability to detoxify CS_2 would lead to higher tissue concentrations and thus, potentially, increased toxicity.

The metabolite responsible for CS_2 hepatotoxicity is believed to be reactive sulfur atoms that covalently bind to cellular macromolecules (Dalvi, 1988). Similarly, the correlation between increased lethality (Green and Hunter, 1985) and increasing binding of ^{35}S – label (Snyderwine and Hunter, 1987) in younger CS_2 -exposed animals is consistent with a role for reactive sulfur. Neurotoxicity of CS_2 results from the formation of thiourea lysine cross-links between neurofilament proteins (DeCaprio et al., 1992; Valentine et al., 1997; Erve et al., 1998).

New Zealand white rabbits (24 per group) inhaled 0, 60, 100, 300, 600 or 1200 ppm CS_2 for 6 h/d on gestation days 6 to 18 (Pathology Associates, 1991). Developmental toxicity (NOAEL = 300 ppm; 930 mg/m^3) was noted at concentrations lower than those associated with significant maternal toxicity (NOAEL = 600 ppm; 1860 mg/ m^3) (Pathology Associates, 1991). The adults did have some slight hematological changes at the 600 ppm level, but the authors questioned the biological significance of these marginal findings. Reduced fetal body weights were noted at 600 and 1200 ppm. Cumulative malformations were increased in the 1200 (3720 mg/m^3) but not 600 ppm group, though there were no significant increases in any specific malformation in any

group. Maternal effects at 1200 ppm included decreased body weight, ataxia, wheezing, and tremors. In an initial range-finding study, exposure to 3000 ppm was associated with significant lethality.

Rats were exposed to 100 mg/m^3 (32 ppm) for 4 hr/d on gestation days 7 and 8, and the embryos explanted to culture medium at day 9.5. Growth of explants of 10 treated and 17 control embryos was monitored for 44 hours. CS_2 at this concentration induced growth retardation in treated embryos relative to controls (Zhao et al., 1997).

In a two-generation study, Tabacova et al. (1983) exposed pregnant Albino rats (30-32 pregnant females per group) to 0.03, 10, 100, or 200 mg/m^3 (0.01, 3, 32, or 64 ppm) CS_2. The two highest dose levels were both teratogenic and maternally neurotoxic. There were no significant adverse effects in the F1 generation at the 2 low dose levels. However, significant increases in teratogenicity were found in the F2 generation at 10 mg/m^3, as well as increased postnatal neurological effects including hypoactivity, mild ataxia and gait disturbances, hind-limb weakness, spinning and tremor (Tabacova et al., 1983). While the overall rate of malformations (club foot, hydrocephalus, microcephalus, generalized edema) exhibited a dose-response trend, with increased effects in the F2 generation, the specific malformations exhibited a less-consistent pattern. For example, while club foot was the predominant malformation in the F1 fetuses (occurring at 100 and 200 mg/m^3); much lower rates of club foot were noted in the F2 generation (including none in the 200 mg/m^3 group). Limitations of the study include a lack of information on chemical purity and exposure methods, lack of concurrent controls, lack of clear dose-response trend, and incomplete reporting on the statistical significance of reported behavioral effects.

Wistar albino rats (32 animals per group) were exposed to 50, 100, or 200 mg/m^3 (16, 32, or 64 ppm) CS_2 for 8 hours per day throughout gestation. There were no statistically significant results in the 50 mg/m^3 group. In the 100 and 200 mg/m^3 groups, there were statistically significant increases in reduced fetal body weights, and reduced post natal body weights for 21 days, which subsequently disappeared. There was an increase in external malformations (hydrocephalus, club foot, and tail deformations) at the two higher doses (Tabacova et al., 1978).

Behavioral effects were examined in the offspring of Lati:CFY rats (8 per group) exposed to 0, 10, 700, or 2000 mg/m^3 CS_2 (3, 230, or 640 ppm) for 6 hours per days over days 7 to 15 of gestation. The two high doses caused significant perinatal mortality. Avoidance conditioning was tested using a bell as a conditional stimulus prior to an electric shock. The animals learned to avoid the shock by jumping onto a pole at the sound of the bell. The latency to jump onto the pole and errors were measured as a means to evaluate avoidance conditioning in the treated versus control animals. The authors reported that there was a dose-related change in avoidance conditioning among male pups over the first 15 days (Lehotsky et al., 1985). While the magnitude of the effect on avoidance conditioning was greater at all doses relative to controls, and at 2000 mg/m^3 compared with 700 mg/m^3, the effect was virtually identical between the 10 and 700 mg/m^3. This lack of dose-response effect raises some question about the significance of this finding.

Effects of low (0.03 and 10 mg/m^3; 0.01 and 3 ppm) prenatal exposures (8 hours per day throughout gestation) of CS_2 were studied in Wistar albino rats. No congenital malformations or significant prenatal effects were found in the 9-11 litters evaluated at each dose. Mortality during postnatal days 10 through 21 was increased in the 10 mg/m^3 group. Delays in the development of visual and auditory function were reported in the higher dose group (Tabacova and Balabaeva, 1980). There was no mention of maternal toxicity in this study.

Several other studies yielded either no teratogenic effects or effects only at maternally toxic exposures. Saillenfait et al. (1989) exposed rats via inhalation to 0, 100, 200, 400, or 800 ppm CS_2 for 6h/d during days 6-20 of gestation. Lower exposures (100 or 200 ppm; 310 or 620 mg/m^3) were not associated with maternal toxicity or adverse effects on the developing embryo or fetus. Higher concentrations (400 or 800 ppm; 1240 or 2480 mg/m^3) yielded a significant reduction of maternal weight gain as well as reductions of fetal body weight and a low incidence of club foot. Significant increases in unossified sternebrae were reported following 800 ppm (2480 mg/m^3) exposures. Nemec et al. (1993) reported no teratogenicity or maternal, developmental, or reproductive toxicity among pregnant CD rats and their offspring following exposure to 125 or 250 ppm (388 or 775 mg/m^3) from 2 weeks prior to mating through gestation day 19. At 500 ppm, dams had decreased body weight gain and food consumption; decreased litter viability but no teratogenic effects were noted. CS_2 was not found to be teratogenic or embryotoxic following intraperitoneal administration to rats on days 1-15 of gestation (Beliles et al., 1980; Hardin et al., 1981). No significant effects were noted in animal inhalation exposures (20 to 40 ppm; 62 to 125 mg/m^3 CS_2) with either rats on days 1-19 of gestation or rabbits on days 1-24 of gestation.

VI. Derivation of Chronic Reference Exposure Level

Study	Johnson *et al.* (1983)
Study population	145 occupationally exposed workers and 212 comparison workers
Exposure method	Discontinuous occupational inhalation exposures (mean of 7.6 ppm and range of 0.6 to 16 ppm)
Critical effects	Reduction in motor nerve conduction velocities (decreased peroneal nerve MCV and sural nerve SVC)
LOAEL	7.6 ppm
NOAEL	Not observed
Exposure continuity	8 hr/day, 5 days/week
Average occupational exposure	2.7 ppm for LOAEL group (7.6 x 10/20 x 5/7)
Benchmark concentration (BMC_{05})	6.86 ppm (continuity-weighted exposure of 2.54 ppm)
Human equivalent concentration	2.54 ppm for BMC_{05} (6.86 x 10/20 x 5/7)
Exposure duration	Mean of 12.1 years (SD 6.9 years)
Subchronic uncertainty factor	1
LOAEL uncertainty factor	Not needed in BMC approach
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Inhalation reference exposure level	0.3 ppm (300 ppb; 0.8 mg/m^3; 800 $\mu g/m^3$)

A benchmark dose analysis was performed on the peroneal MCV data. The NIOSH exposure data were regrouped into 8 geometrically spaced dose groups (Table 1).

Table 1. Peroneal MCV data used for benchmark dose modeling

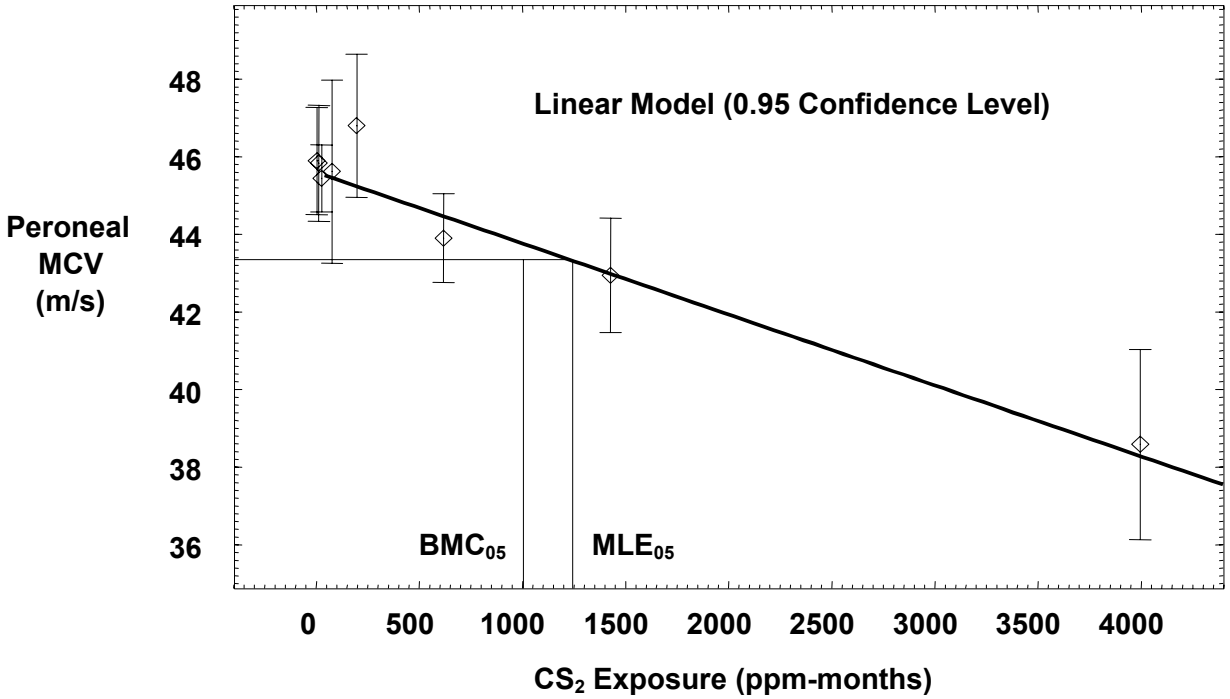
Exposure (ppm-months)	***Subjects***	***Peroneal MCV (m/s)***	
		Mean	***Std. Dev.***
3.8 (2 - 6)	32	45.9	3.8
13.1 (6 - 16)	61	45.8	5.8
26.5 (16-44)	140	45.4	5.2
77.3 (44-122)	17	45.6	4.6
197 (122 – 336)	17	46.8	3.6
619 (336 – 929)	54	43.9	4.2
1428 (929-2563)	61	42.9	5.8
3997 (2563 – 7075)	19	38.6	5.1

Model fitting was conducted with U.S. Environmental Protection Agency BMDS Benchmark Dose Software, Version 1.3. Four continuous data models were compared: linear, polynomial (v. 2.1), power (v. 2.1) and hill (v. 2.1) models. All four models adequately fit the data set (Table 2).

Table 2. Benchmark dose modeling results

Model	***MLE_{05} (ppm-mo)***	***BMC_{05} (ppm-mo)***	***p value***
Linear	1245	1005	0.84
Polynomial	1100	736	0.78
Hill	1092	670	0.65
Power	1245	1005	0.58

The BMC_{05} from the best-fitting linear model was used. An occupational BMC_{05} of 6.9 ppm was derived by dividing the 1005 ppm-month value by the average exposure duration of 145 months (12.1 years). The time-weighted average value was thus 2.5 ppm (6.9 ppm x 10/20 x 5/7).



The U.S. EPA (1995) based its RfC of 700 μg/m^3 on the same study but used a BMC_{10} and included a Modifying Factor (MF) of 3 for database deficiencies. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors are not used by OEHHA. In addition OEHHA prefers use of a BMC_{05} since in practice it tends to be closer to the NOAEL while the BMC_{10} is often closer to the LOAEL (OEHHA, 2000).

For comparison, 50 ppm was a 13 week NOAEL in rats for axonal swelling (Sills *et al*., 1998). The equivalent continuous exposure is 8.9 ppm. Use of an RGDR of 1, an interspecies UF of 3, a subchronic UF of 3, and an intraspecies UF of 10 results in a REL of 90 ppb.

VII. Data Strengths and Limitations for Development of the REL

The major strengths of the REL for carbon disulfide are the use of human data, the observation of a dose-response effect, and the duration of exposures. The major uncertainties are the poor quantitation of actual exposure magnitude over time and the limited nature of the health effects studies which have been conducted.

VIII. Potential for Differential Impacts on Children's Health

The data available on the developmental toxicity of carbon disulfide are equivocal. Several studies reported that adverse developmental effects are only noted with exposures exceeding 100 ppm, while Tabacova and Balabaeva (1980) and Lehotsky et al. (1985) reported transient effects at levels as low as 10 mg/m^3 (3 ppm). The results of these two studies are not consistent with the database as a whole. While further research into behavioral effects of low concentrations of CS_2 would better clarify the risks associated with such exposures, no adverse effects have been reported at concentrations below the REL of 800 µg/m^3 (300 ppb).

IX. References

Aaserud O, Gjerstad L, Nakstad P, Nyberg-Hansen R, Hommeren OJ, Tvelt B, Russell D, and Rootwelt K. 1988. Neurological examination, computerized tomography, cerebral blood flow and neuropsychological examination in workers with long-term exposure to carbon disulfide. Toxicology 49(2-3):277-282.

Aaserud O, Hommeren OJ, Tvedt B, Nakstad P, Mowe G, Efskind J, Russell D, Jorgensen EB, Nyberg-Hansen R, and Rootwelt K. 1990. Carbon disulfide exposure and neurotoxic sequelae among viscose rayon workers. Am. J. Ind. Med. 18(1):25-37.

Aaserud O, Russell D, Nyberg-Hansen R, Rootwelt K, Jorgensen EB, Nakstad P, Hommeren OJ, Tvedt B, and Gjerstad L. 1992. Regional cerebral blood flow after long-term exposure to carbon disulfide. Acta Neurol. Scand. 85(4):266-271.

Bao YS, Cai S, Zhao SF, Xhang XC, Huang MY, Zheng O, Jiang Y. 1991. Birth defects in the offspring of female workers occupationally exposed to carbon disulfide in China. Teratology 43:451-452.

Beliles RP, Brusick DJ, Mecler FJ. 1980. Teratogenic-mutagenic risk of workplace contaminants. Litton Bionetics, Kensington, MD. NIOSH 210-77-0047.

Bortkiewicz A, Gadzicka E, Szymczak W. 2001. Cardiovascular disturbances in workers exposed to carbon disulfide. Appl Occup Environ Hyg 16(4):455-63.

Bond EJ, Butler WH, De Matteis F, and Barnes JM. 1969. Effects of carbon disulphide on the liver of rats. Br. J. Ind. Med. 26(4):335-337.

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System. (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Cirla AM, Bertazzi PA, Tomasini M, Villa A, Graziano C, Invernizzi R, Gilioli R. 1978. Study of endocrinological functions and sexual behaviour in carbon disulphide workers. Med. Lav. 69(2):118-129.

Clerici WJ, and Fechter LD. 1991. Effects of chronic carbon disulfide inhalation on sensory and motor function in the rat. Neurotoxicol. Teratol. 13(3):249-255.

Colombi A, Maroni M, Picchi O, Rota E, Castano P, and Foa V. 1981. Carbon disulfide neuropathy in rats. A morphological and ultrastructural study of degeneration and regeneration. Clin. Toxicol. 18(12):1463-1474.

Dalvi RR. 1988. Mechanism of the neurotoxic and hepatotoxic effects of carbon disulfide. Drug Metabol Drug Interact 6(3-4):275-84.

DeCaprio AP, Spink DC, Chen X, Fowke JH, Zhu M, Bank S. 1992. Characterization of isothiocyanates, thioureas, and other lysine adduction products in carbon disulfide-treated peptides and protein. Chem Res Toxicol. 5(4):496-504.

Egeland GM, Burkhart GA, Schnorr TM, Hornung RW, Fajen JM, and Lee ST. 1992. Effects of exposure to carbon disulphide on low density lipoprotein cholesterol concentration and diastolic blood pressure. Br. J. Ind. Med. 49(4):287-293.

Erve JC, Amarnath V, Graham DG, Sills RC, Morgan AL, Valentine WM. 1998. Carbon disulfide and N,N-diethyldithiocarbamate generate thiourea cross-links on erythrocyte spectrin in vivo. Chem Res Toxicol. 11(5):544-9.Eskin TA, Merigan WH, and Wood RW. 1988. Carbon disulfide effects on the visual system. II. Retinogeniculate degeneration. Invest. Ophthalmol. Vis. Sci. 29(4):519-527.

Fajen J, Albright B, and Leffingwell SS. 1981. A cross-sectional medical and industrial hygiene survey of workers exposed to carbon disulfide. Scand. J. Work Environ. Health. 7(Suppl 4):20-27.

Foa V, Cassitto MG, and Forzi M. 1976. Mental performance and personality disorders among workers exposed to carbon disulphide: Comparison between two different rayon plants. In: Adverse Effects of Environmental Chemicals and Psychotrophic Drugs, Neurophysiological and Behavioural Tests. Vol. 2. pp. 173-182.

Gottfried MR, Graham DG, Morgan M, Casey HW, and Bus JS. 1985. The morphology of carbon disulfide neurotoxicity. Neurotoxicology. 6(4):89-96.

Green EC, Hunter A (1985). Toxicity of carbon disulfide in developing rats: LD50 values and effects on the hepatic mixed-function oxidase enzyme system. Toxicol Appl Pharmacol 78(1):130-138.

Hanninen H, Nurminen M, and Tolonen M. 1978. Psychological tests as indicators of excessive exposure to carbon disulfide. Scand. J. Psychol. 19:163-174.

Hernberg S, Partanen T, Nordman CH, and Sumari P. 1970. Coronary heart disease among workers exposed to carbon disulphide. Br. J. Ind. Med. 27:313-325.

Hirata M, Ogawa Y, Okayama A, and Goto S. 1992. A cross-sectional study on the brainstem auditory evoked potential among workers exposed to carbon disulfide. Int. Arch. Occup. Environ. Health 64(5)321-324.

HSDB. 1995. Hazardous Substances Data Bank. (Edition of January 1995). National Library of Medicine, Bethesda, MD (TOMES® CD-Rom Version). Denver, CO: Micromedex, Inc.

Jirmanova I, and Lukas E. 1984. Ultrastructure of carbon disulphide neuropathy. Acta Neuropathologica 63(3):255-263.

Johnson BL, Boyd J, Burg JR, Lee ST, Xintaras C, and Albright BE. 1983. Effects on the peripheral nervous system of workers' exposure to carbon disulfide. Neurotoxicology 4(1)53-65.

Knobloch K, Stetkiewicz J, and Wronska-Nofer T. 1979. Conduction velocity in the peripheral nerves of rats with chronic carbon disulphide neuropathy. Br. J. Ind. Med. 36(2):148-152.

Kotseva K, Braeckman L, Duprez D, De Bacquer D, De Buyzere M, Van De Veire N, Vanhoorne M. 2001a. Decreased carotid artery distensibility as a sign of early atherosclerosis in viscose rayon workers. Occup Med (Lond) 51(4):223-9.

Kotseva K. 2001b. Occupational exposure to low concentrations of carbon disulfide as a risk factor for hypercholesterolaemia. Int Arch Occup Environ Health 74(1):38-42.Lancranjan I, Popescu HI, Klepsch I. 1969. Changes of the gonadic function in chronic carbon disulphide poisoning. Med. Lav. 60(10):566-571.

Lancranjan I. 1972. Alterations of spermatic liquid in patients chronically poisoned by carbon disulphide. Med. Lav. 63(1):29-33.

Lehotsky K, Szeberenyi JM, Ungvary G, Kiss A (1985). Behavioural effects of prenatal exposure to carbon disulfide and to aromatol in rats. Arch Toxicol Suppl 8:442-446.

Lewis JG, Graham DG, Valentine WM, Morris RW, Morgan DL, Sills RC. 1999. Exposure of C57BL/6 mice to carbon disulfide induces early lesions of atherosclerosis and enhances arterial fatty deposits induced by a high fat diet. Toxicol. Sci. 49(1):124-132.

MacMahon B, and Monson RR. 1988. Mortality in the US rayon industry. J. Occup. Med. 30(9):698-705.

Maroni M, Colombi A, Rota E, Antonini C, Picchi O, Foa V, Caimi L, Tettamanti G, and Castano P. 1979. Biochemical and morphological investigations on nervous tissue of rats inhaling carbon disulphide. Med. Lav. 70(6):443-451.

OEHHA. 2000. Office of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program Risk Assessment Guidelines. Part III. Technical Support Document for the Determination of Noncancer Chronic Reference Exposure Levels. Available on-line at http://www.oehha.ca.gov

Nemec MD, Holson JF, Naas DJ, Shour MH, Gerhart JM (1993). An assessment of reproduction in female rates exposed to carbon disulfide vapor. Teratol Soc Abstracts 47:430.

Pathology Associates (1991). Developmental inhalation toxicity study of carbon disulfide in the New Zealand white rabbit. January 31, 1991. Pathology Associates, Frederick, MD. Project Number 2100-202.

Price B, Berner T, Henrich RT, Stewart JM, and Moran EJ. 1996. A Benchmark Concentration for carbon disulfide: Analysis of the NIOSH carbon disulfide exposure database. Regul. Toxicol. Pharmacol. 24:171-176.

Ruijten MW, Salle JH, Verberk MM, and Muijser H. 1990. Special nerve functions and colour discrimination in workers with long term low level exposure to carbon disulphide. Br. J. Ind. Med. 47(9):589-595.

Ruijten MW, Salle HJ, and Verberk MM. 1993. Verification of effects on the nervous system of low level occupational exposure to CS_2. B. J. Ind. Med. 50(4):301-307.

Saillenfait AM, Bonnet P, De Caurriz J (1989). Effects of inhalation exposure to carbon disulfide and its combination with hydrogen sulfide on embryonic and fetal development in rats. Toxicol Lett 1989 Jul;48(1):57-66.

Sills RC, Harry GJ, Morgan DL, Valentine WM, Graham DG. 1998. Carbon disulfide neurotoxicity in rats: V. Morphology of axonal swelling in the muscular branch of the posterior tibial nerve and spinal cord. Neurotoxicology 19(1):117-127.

Simmons JE, Sloane RA, and Van Stee EW. 1988. Hepatic cholesterol metabolism as a function of carbon disulfide concentration and treatment with phenobarbital. Am. Ind. Hyg. Assoc. J. 49(9):427-433.

Snyderwine EG, Hunter A (1987). Metabolism and distribution of 14C- and 35S-labeled carbon disulfide in immature rats of different ages. Drug Metab Dispos 15(3):289-294

Sokal JA. 1973. Effect of chronic exposure to carbon disulphide upon some components of the electron transport system in rat liver microsomes. Biochem. Pharmacol. 22(1):129-132.

Szendzikowski S, Karasek M, Stetkiewicz J, and Wronska-Nofer T. 1973. Ultrastructure of the peripheral nerve in rats chronically exposed to carbon disulphide, preliminary report. Folia Histochemica et Cytochemica 11(3):353-354.

Tabacova S, Balabaeva L (1980). Subtle consequences of prenatal exposure to low carbon disulphide levels. Arch Toxicol Suppl. 4:252-4.

Tabacova S, Hinkova L, Balabaeva L (1978). Carbon disulfide teratogenicity and post natal effects in rat. Toxicol Lett 2:129-133.

Tabacova S, Nikiforov B, Balabaeva L (1983). Carbon disulphide intrauterine sensitization. J Appl Toxicol 3(5):223-229.

Tiller JR, Schilling RS, and Morris JM. 1968. Occupational toxic factors in mortality from coronary heart disease. Br. Med. J. 4:407-411.

Tolonen M, Nurminen M, and Hernberg S. 1979. Ten-year coronary mortality of workers exposed to carbon disulfide. Scand. J. Work Environ. Health 5(2):109-114.

USDHHS. 1994. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Toxicological Profile for Carbon Disulfide. Draft.

U.S. Environmental Protection Agency. 1995. Carbon Disulfide. CASRN 75-15-0. Integrated Risk Information System, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency. Valentine WM, Amarnath V, Graham DG, Morgan DL, Sills RC. 1997. CS_2-mediated cross-linking of erythrocyte spectrin and neurofilament protein: dose response and temporal relationship to the formation of axonal swellings. Toxicol Appl Pharmacol. 142(1):95-105.Vanhoorne M, De Bacquer D, and De Backer G. 1992. Epidemiological study of the cardiovascular effects of carbon disulphide. Int. J. Epidemiol. 21(4):745-752.

Vanhoorne MH, Ceulemans L, De Bacquer DA, De Smet FP (1995). An epidemiologic study of the effects of carbon disulfide on the peripheral nerves. Int J Occup Environ Health 1(4):295-302.

Wagar G, Tolonen M, Tanner P, and Helpio E. 1983. Serum gonadotropins and testosterone in men occupationally exposed to carbon disulfide. J. Toxicol. Environ. Health 11(4-6):691-701.

Wronska-Nofer T. 1973. Disturbances of lipids metabolism in rats in dependence upon carbon disulphide concentrations in the air. Med. Lav. 64(1):8-12.

Wronska-Nofer T, Klimczak J, Wisniewska-Knypl JM, Jajte J, and Opalska B. 1986. Combined effect of ethanol and carbon disulphide on cytochrome P-450 mono-oxygenase, lipid peroxidation and ultrastructure of the liver in chronically exposed rats. J. Appl. Toxicol. 6(4):297-302.

Zhao SF, Zhang XC, Zhang LF, Zhou SS, Zhang F, Wang QF, Wang YL, Bao YS (1997). The evaluation of developmental toxicity of chemicals exposed occupationally using whole embryo culture. Int J Dev Biol 41(2):275-82.

Zhou SY, Liang YX, Chen ZQ, and Wang YL. 1988. Effects of occupational exposure to low-level carbon disulfide (CS_2) on menstruation and pregnancy. Ind. Health 26(4):203-214.